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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,202	01/22/2004	Guping Tang	4249-0115P	2330

2292 7590 06/05/2007

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EXAMINER	
MAKAR, KIMBERLY A	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
06/05/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/761,202	TANG ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-19 and 21-35* is/are pending in the application.

4a) Of the above claim(s) *30-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-19 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Cancellation of claims 3-4, and 20 in the amendment dated 3/21/07 is acknowledged. Currently claims 1-2, 5-19; 21-35 are pending. Claims 30-35 are withdrawn. Claims 1-9,11-12, 16-18, 20-25 and 29 are rejected under 102(b) as being taught by Kosak et al (Patent Publication US2001/0034333) and claims 1-4, 8-20 and 24-20 as being taught by Cheng et al (US Patent Publication US2004/0077595). Amendments to the claims in the response dated 3/21/07 is acknowledged. Any rejection not maintained in this office action is withdrawn.

Claim Objections

2. Claims 1 and 16 are objected to because of the following informalities: Claims 1 and 16 use the alternate spelling for "polyethylenimine" of "polyethyleneimine" in the newly amended phrases. The entirety of the specification and claim set use the spelling "polyethylenimine." It would be remedial to amend the alternate spellings in order to maintain consistency throughout the specification and claims. Appropriate correction is required

For the purposes of prosecution the following is defined:

3. "Polymer." The specification fails to define polymer. The *Columbia Encyclopedia* teaches:

4. Chemical compound with high molecular weight consisting of a number of structural units linked together by covalent bonds (see chemical bond). The simple molecules that may become structural units are themselves called monomers; two monomers combine to form a dimer, and three monomers, a trimer. A structural unit is a group having two or more bonding sites. A bonding site may be created by the loss of an atom or group, such as H or OH, or by the breaking up of a double or triple bond, as when

ethylene, $H_2C=CH_2$, is converted into a structural unit for polyethylene, $-H_2C-CH_2-$. In a linear polymer, the structural units are connected in a chain arrangement and thus need only be bifunctional, i.e., have two bonding sites. When the structural unit is trifunctional (has three bonding sites), a nonlinear, or branched, polymer results. Ethylene, styrene, and ethylene glycol are examples of bifunctional monomers, while glycerin and divinyl benzene are both polyfunctional. Polymers containing a single repeating unit, such as polyethylene, are called homopolymers. Polymers containing two or more different structural units, such as phenol-formaldehyde, are called copolymers. All polymers can be classified as either addition polymers or condensation polymers. An addition polymer is one in which the molecular formula of the repeating structural unit is identical to that of the monomer, e.g., polyethylene and polystyrene. A condensation polymer is one in which the repeating structural unit contains fewer atoms than that of the monomer or monomers because of the splitting off of water or some other substance, e.g., polyesters and polycarbonates. Many polymers occur in nature, such as silk, cellulose, natural rubber, and proteins. In addition, a large number of polymers have been synthesized in the laboratory, leading to such commercially important products as plastics, synthetic fibers, and synthetic rubber. Polymerization, the chemical process of forming polymers from their component monomers, is often a complex process that may be initiated or sustained by heat, pressure, or the presence of one or more catalysts. polymer. (2004). In *The Columbia Encyclopedia* . Retrieved May 22, 2007, from http://www.xreferplus.com/entry/4294040polymer. (2004). In *The Columbia Encyclopedia* . Retrieved May 22, 2007, from DISPLAYURL "polymer." *The Columbia Encyclopedia* . 2004. Xreferplus. 22 May 2007 <DISPLAYURL>. *The Columbia Encyclopedia* , 2004, s.v. "polymer," DISPLAYURL (accessed May 22, 2007).

5. Thus a "polymer" is composed of individual "monomer" subunits. A "dimer" is a "polymer" comprised of two "monomer" subunits.

6. "Copolymer." The specification fails to teach a definition for the term "copolymers." As referenced above, the Columbia Encyclopedia teaches that a "copolymer" is a polymer containing two or more different structural units.

"Biodegradable." The specification fails to define biodegradable. The specification implies that the presence of ester bonds confers biodegradable qualities to the polymers (page 4, lines 8-11). Thus any polymer comprising ester bonds is defined as "biodegradable".Claims 1 and 16 are broad, and as written could read on a large variety of configurations including:

alternating monomer units of CD-PEI-CD-PEI-CD-PEI

or could read on alternating units of polymers: PEI-PEI-CD-PEI-PEI-CD-PEI-PEI

or could read on copolymers comprising: PEI-PEI-CD-CD-PEI-PEI-CD-CD-PEI-PEI

Additionally, the phrase "polyethylenimine is a linear polymer" is a limitation directed towards the polyethylenimine, not the entire copolymer, thus the entire copolymer is not required to be linear, but reads on branch, block, or graft polymers. Furthermore, the claim explicitly states "wherein the polyethylenimine is a linear polymer", thus suggesting that there are at least two PEI monomers as a dimer in linear form as a condition for the claim.

The following rejections are necessitated by applicant's amendments dated 3/21/07.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, and 5-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1, amended 3/21/07, recites a biodegradable copolymer suitable for delivering a nucleic acid molecule to a cell, comprising a cyclodextrin "modified at no more than two positions" to allow attachment "to no more than two polyethyleneimine molecules." The specification as originally filed does not provide support for the claimed limitation "modified at no more than two

positions" nor "to no more than two polyethyleneimine molecules." The instant claims now recite a limitation, which was not clearly disclosed in the specification as filed, and now changes the scope of the instant disclosure as filed.

8. In the response dated 3/21/07, Applicant's contend that the limitation is supported "in Figure 1 of the present specification which explicitly shows modification of the activating agent at two positions. It is also implicit in the description that an end group CD of the PEI-CD copolymer would have only one activating agent bonded thereto." (Page 11 of applicant's response).

9. The Examiner disagrees with this argument. Simply because Figure 1 shows one embodiment in which two positions are modified on the cyclodextrin does not support the limitation that "no more than two" are modified. Such a limitation recited in the present claims, which did not appear in the specification as filed, introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112. THIS IS A NEW MATTER REJECTION.

Claim Rejections - 35 USC § 103

10. The following rejection is necessitated by applicant's amendments dated 3/21/07.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-2, 5-9, 11-12, 16-18, 21-25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kosak et al (US Patent Publication No: US 2001/0034333) and Davis et al (US Patent No: 6,509,323). Claims 1-2, 5-9, and 11-12 recite a biodegradable copolymer suitable for delivering a nucleic acid molecule to a cell, the copolymer comprising polyethylenimine (PEI) linked to a cyclodextrin, wherein the PEI is a linear polymer having a molecular weight of less than 10,000 Daltons, and wherein the cyclodextrin is modified at no more than two positions by an activating agent to allow attachment to no more than two polyethylenimine molecules. The copolymer is further limited to have a net positive charge and being capable of complexing with negatively charged nucleic acid molecules (claim 2), wherein the PEI has a molecule weight of less than about 5000 Daltons (claim 5), or less than about 2000 Daltons (claim 6) or from about 600 to 2000 Daltons (claim 7). The polymer is further limited wherein the cyclodextrin is beta-cyclodextrin (claim 8), and where the agent is selected fro the group consisting of beta-1,1' carbonyldiimidazole, benzotriazole carbonate, N,N'-

disuccinimidyl carbonate, chloroformates, N'-hydroxysuccinimidyl chloroformate, and carbonylimidazole (claim 9). The copolymer is further limited wherein the PEI is cross-linked to cyclodextrin via a carbonyl group (claim 11), and has ester bonding (claim 12). Claims 16-18, and 21-25 recite a method for synthesizing a biodegradable copolymer comprising the steps of: reacting cyclodextrin with an agent to bond with cyclodextrin at no more than two positions on the cyclodextrin to form an activated cyclodextrin; and (b) reacting the activated cyclodextrin with a low linear PEI having a molecular weight of less than 10,000 Daltons to form a biodegradable copolymer comprising polyethylenimine linked to cyclodextrin wherein no more than two PEI molecules are attached to each cyclodextrin (claim 16) wherein the cyclodextrin is beta-cyclodextrin (claim 17). The method is further limited wherein the agent is selected fro the group consisting of beta-1,1' carbonyldiimidazole, benzotriazole carbonate, N,N'-disuccinimidyl carbonate, chloroformates, N'-hydroxysuccinimidyl chloroformate, and carbonylimidazole (claim 18). The method is further limited wherein the PEI has a molecule weight of less than about 5000 Daltons (claim 21), or less than about 2000 Daltons (claim 22) or from about 600 to 2000 Daltons (claim 23). The method is further limited wherein the PEI is cross-linked to cyclodextrin via a carbonyl group (claim 24), and has ester bonding (claim 25). Claim 29 recites the biodegradable copolymer synthesized by the method according to claim 16.

14. This rejection is based on the alternate reading in which the base claims 1 and 16 read on a copolymer comprising: alternating monomer units of CD-PEI-CD-PEI-CD-PEI or PEI-PEI-CD-CD-PEI-PEI-CD-CD-PEI-PEI.

15. Kosak et al (US Patent Publication No: US2001/0034333) teaches compositions and methods of making said compositions comprising cyclodextrin polymers for carrying drugs and other active agents (see abstract). Specifically Kosak teaches that the polymer can be heteropolymers (copolymers) comprising a cyclodextrin and a "spacer" (page 8, paragraph 0115). Kosak teaches that the cyclodextrin polymers comprising the spacers are used to overcome steric hindrance of subsequent binding reactions.

> [T]he intermediate can function as a polymer "backbone" to which many cyclodextrin dimers, trimers or polymers are covalently coupled to form a larger polymer. The intermediate can be included with cyclodextrin derivatives as another monomer to be copolymerized with the cyclodextrin derivatives (i.e. heteropolymer), to provide improved structural properties, increase solubility or lower toxicity. The intermediate substance may also provide the advantage of additional coupling sites and thereby increase the number of covalently coupled cyclodextrin derivates within a polymer carrier. The intermediate can able introduce certain other desirable properties, such a s a positive or negative net charge, more efficient light energy transfer for photodynamic therapy...Examples of such biologically neutral intermediate coupling substances are certain proteins, polypeptides, polyamino acids, serum albumins, glycoproteins, lipoproteins, nucleic acid polymers, DNA, RNA, amino sugars, glucosamines, polysaccharides, lipopolysaccharides, amino polysaccharides, polyglutamic acids, polylysines, polyacrylamines, nylons, poly(allylamines), lipids, glycolipids, and suitable synthetic polymers, especially biopolymers, resins, and surfactants, as well as suitable derivatives of these substances. Also included as suitable intermediate coupling substances are the polymers disclosed in U.S. Pat. No. 4,645,646. Also preferred as intermediates are N-(2-hydroxypropyl)methacrylamide (HPMA), HPMA derivatives, poly cyanoacrylates such as poly(butyl cyanoacrylate), poly(isobutyl or isohexyl cyanoacrylate), polyethylene glycol (PEG), any PEG derivatives, poly (D,L-lactic-coglycolic acid) (PLGA), PLGA derivatives, dendrimers and poly (D,L-lactide)-block-methoxy-polyethylene glycol (Diblock). Page 8, paragraphs 0014-0017.

16. Kosak teaches that the DNA binding substance polyethylenimine (PEI) can be combined into the copolymer (page 4, paragraph 0055; page 18, paragraph 0284), and uses a low molecular weight PEI, with a molecular weight of 800, in a copolymer with cationic cyclodextrin polymers in the working example Preparation XIX on page 24. Absent evidence to the contrary, the molecular weight of 800 taught by Kosak is in

Daltons. Kosak teaches that the cyclodextrins used in the copolymers can be beta-cyclodextrin (page 4, paragraph 63), and that the cyclodextrin is treated to become cationic (net positive charge) by the addition of primary, secondary and tertiary amines (page 10, paragraph 0136; page 23, paragraph 0347-0349). Kosak further teaches that the copolymers can be coupled to bioactive agents, particularly DNA (page 3, paragraph 0040). Kosak further teaches that the agent responsible that can provide the bio-compatible linkages for synthesizing the cyclodextrin polymers of the instant invention includes the chloroformate ethyl chloroformate (page 7, paragraph 0106). Furthermore, Kosak teaches that the copolymer can be formed via a carbonyl group, and can comprise ester bonds (page 10, paragraph 0136). Kosak teaches an ester bond is an example of a "biocleavable linkage or bond" (page 3, paragraph 0042-0044). Thus Kosak teach his polymers are biodegradable in light of the current specification.

17. Kosak also teaches methods of making a biodegradable copolymer by treating cyclodextrin with 1,4 butanediol diglycidyl ether (an agent) to form a modified or activated cyclodextrin and adds the cyclodextrin to a low molecular weight polyethylenimine (see Preparation XIX on pages 23-24). Kosak teaches that the polymer can be heteropolymers (copolymers) comprising a cyclodextrin and a "spacer" which forms part of the backbone of the polymer (page 8, paragraph 0115, and above). Kosak teaches that the DNA binding substance polyethylenimine (PEI) can be can be combined into the copolymer (page 4, paragraph 0055, and page 8, paragraph 0014-0017), and uses a low molecular weight PEI, with a molecular weight of 800, in a copolymer with cationic cyclodextrin polymers in Preparation XIX on page 24.

18. Kosak's invention reads on CD monomers, dimers, and trimers etc:

For this invention, individual cyclodextrin (CD-monomer) derivatives function as the primary building structures, or components, or units used to synthesize the water-soluble (or colloidal) cyclodextrin polymer carriers. Paragraph 0070.

19. Kosak teaches that the cyclodextrins are coupled in a process known as "capping":

Capping is a type of derivatizing defined herein as **coupling any suitable chemical** "capping substance" **to two** or more **sites on the CD molecule** so that the substance spans the area between the coupled sites. Preferably, the capping substance spans across one of the end openings of the CD molecule and thereby stops the passage of a guest molecule through the capped CD molecule. Paragraph 0206

The CD's used herein can be suitably complexed with one or more guest molecules and/or derivatized and/or capped before, **during** or after their **incorporation into the water-soluble CD polymer carrier of the instant invention**. In addition, the derivatizing and/or capping can be a done to produce CD's with the desired substances **coupled to specific locations on the CD molecule**. (paragraph 0206 and 0208)

Preferably, **the capping substance is coupled** at the primary or secondary "end" of the CD molecule, **forming a bridge across** either (or both) opening(s) that includes suitable hydrophobic groups in the capping substance. **The capping substances can be coupled directly to available hydroxyls on the CD, or they can be coupled to** suitable functional groups such as; diamino (or triamino), compounds to iodinated CD, or azido compounds to sulfonylated hydroxyls, and/or through **"spacers"** added to the CD. Paragraph 0210.

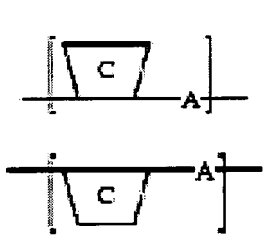
Alternatively, other amino compounds have been coupled to the oxidized CD such as hydrazine, adipic add dihydrazide, glutamic acid, beta-phenylethylamine, laurylamine and cystamine. **Many other useful amino compounds can be coupled to the oxidized CD or CD-block such as** polypeptides, 6-amino-N-hexanoic acid, arginine, protamines, N-(2-aminoethyl)-1,3-propanediamine (AEPD), **polyethylenimine (PEI)** and nucleic acids. Paragraph 0284. (Emphasis Added).

20. Kosak teaches that the cyclodextrins used in the copolymers can be beta-cyclodextrin (page 4, paragraph 63), and that the cyclodextrin is treated to become cationic (net positive charge) by the addition of primary, secondary and tertiary amines (page 10, paragraph 0136, page 23, paragraph 0347-0349). Kosak further teaches that the copolymers can be coupled to bioactive agents, particularly nucleic acid agents

including RNA, DNA, oligonucleotides, antisense oligonucleotides, as well as synthetic and modified nucleic acids (page 3, paragraphs 0040-0041). Kosak further teaches that the agent responsible that can provide the bio-compatible linkages for synthesizing the cyclodextrin polymers of the instant invention includes the chloroformate ethyl chloroformate (page 7, paragraph 0106). Furthermore, Kosak teaches that the biodegradable copolymer is formed via a carbonyl group, and comprises ester bonds (page 10, paragraph 0136).

21. Thus Kosak teaches that activated beta-cyclodextrin can form biodegradable copolymers, and that polymers can be in the backbone of the copolymer (Page 8, paragraphs 0014-0017) and that PEI with a molecular weight of 800 Daltons conjugated to cyclodextrins in the specific working example of Preparation XIX. However, Kosak does not teach that the PEI and cyclodextrin copolymer is a linear polymer, nor that the cyclodextrin is modified at no more than two positions by an activating agent to allow attachment to no more than two polyethylenimine molecules.

22. Davis et al (US Patent 6,509,323) teaches linear cyclodextrin copolymers integrated into a polymer backbone, which may be used as a delivery vehicle of various therapeutic agents (see abstract). Davis teaches the basic cyclodextrin copolymer unit comprises the formula:

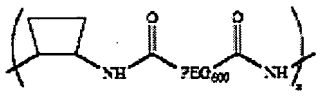


23. Davis teaches, "[I]n formula Ia and Ib, C is a substituted or unsubstituted cyclodextrin monomer and A is a comonomer bound, i.e. covalently bound, to cyclodextrin C. Polymerization of a cyclodextrin monomer C precursor with a comonomer A precursor results in a linear cyclodextrin copolymer of the invention. Within a single linear cyclodextrin copolymer of the invention, the cyclodextrin monomer C unit may be the same or different and likewise, the comonomer A may be the same or different" (column 4, lines 20-36). Davis teaches that C is beta cyclodextrin (column 4, line 44), and the comonomer A precursor "may be any straight chain or branched, symmetric or asymmetric compound which upon reaction with a cyclodextrin monomer precursor, as described above, linked two cyclodextrin monomers together....Accordingly, combinations of such linkages may exist in the final copolymer" Column 6 lines 30- column 7 line 1). Examples of comonomers A include "cystamine, 1,6-diaminohexane, diimidazole, dithioimidazole, spermine, dithiospermine, dihistidine, succinimide...and imidates" (column 7, lines 9-16).

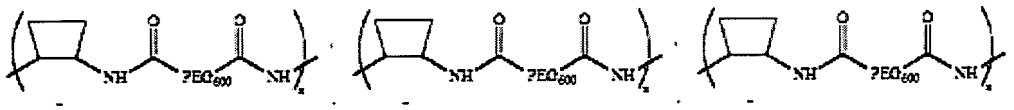
24. Davis teaches that the cyclodextrin is modified, such that only 2 positions are chemically modified:

25. A cyclodextrin monomer precursor may be further chemically modified (e.g. halogenated, aminated) to facilitate or affect copolymerization of the cyclodextrin monomer precursor with a comonomer A precursor, as described below. Chemical modification of a cyclodextrin monomer precursor allows for polymerization at only two positions on each cyclodextrin moiety, i.e. the creation of a bifunctional cyclodextrin moiety (column 4 line 61- column 5 line 1).

26. Davis further teaches that the linear cyclodextrin copolymer "may be crosslinked to a polymer to form, respectively, a crosslinked cyclodextrin copolymer...The polymer may be any polymer capable of crosslinking with a linear or linear oxidized cyclodextrin copolymer of the invention (e.g. polyethylene glycol (PEG) polymer, polyethylene polymer)...A crosslinked linear cyclodextrin copolymer of the invention may be prepared by reacting a linear cyclodextrin copolymer with a polymer in the presence of a crosslinking agent" (column 14, lines 25-43). Davis teaches the production of a cyclodextrin-Polyethylene glycol (PEG) linear copolymer in example 12:



27. A linear polymer comprising and X=3 of the above polymer would have the following structure:

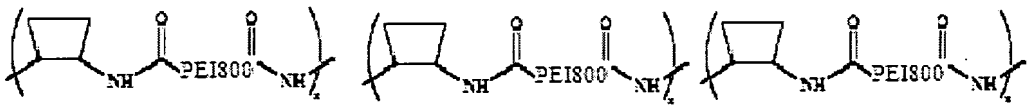


28. Davis teaches that cyclodextrin polymers are used for delivery of therapeutic compounds, through hydrophobic interactions or non-covalent interactions, such as

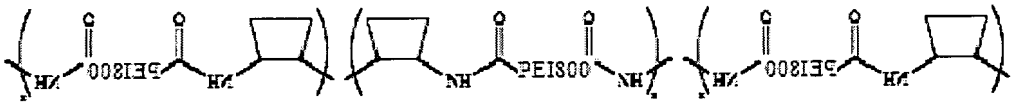
oligonucleotides (column 2, lines 11-17), but that these copolymers in the art contain cyclodextrins as sidechains off of a linear polymer main chain, and that the main chain cyclodextrin polymers in the art are biodegradable, but are cyclic "necklace-type" or pendant polymers. Davis teaches his method is capable of providing linear polymers wherein the cyclodextrin moiety is not a side chain nor pendant moieties (column 2, lines 29-67).

29. A skilled artisan would have been motivated to combine the teaching of Kosak on a biodegradable copolymer and methods of making said copolymer comprising a polyethylenimine of less than 10,000 Daltons and a modified beta-cyclodextrin, wherein the intermediate spacer molecules are part of the backbone of the polymer with the teaching of Davis et al on a method of making a modified cyclodextrin linear copolymer comprising activated cyclodextrin such that only two positions are capable of forming attachments, wherein the copolymer comprises both the modified cyclodextrin and a polymer (such as PEG as in example 12 or a polyethylene polymer (Davis column 14, lines 25-43)) because cyclodextrin and polyethylenimine are well known polymers as therapeutic carriers of nucleic acids, for the expected benefit of producing a biodegradable linear copolymer of a low molecular weight polyethylenimine and cyclodextrin, thus producing a new nucleic acid carrier of two polymers well known in the art for carrying nucleic acids fashioned in a stable linear structure that would be easily biodegradable by cells and the body, allowing the polymer to deliver the nucleic acids to target cells but then cleared from the body at a faster rate than polymers of the art. A polymer comprising a low molecular weight PEI copolymer as taught by Kozak,

and an activated linear cyclodextrin of David (who teaches a polyethylene polymer can be exchanged for the PEG of his example) would have the structures:



Or



30. It would have been obvious to the skilled artisan to combine the teaching of Kosak on a method of making a low molecular weight PEI and cyclodextrin copolymer with the teaching of Davis on a linear copolymer comprising a modified cyclodextrin and a polyethylene, wherein the cyclodextrin is only capable of attachment to two molecules, because both cyclodextrin and low molecular weight polyethylenimine are well known carriers of therapeutics and the combination of the two in linear form would be an advance over the art, as Davis teaches that previous cyclodextrin polymers are not in linear polymers, but side chain or pendant moieties. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

31. Claims 10, 13-15, 26-28 and rejected under 35 U.S.C. 103(a) as being unpatentable over Kosak et al (US Patent Publication No: US 2001/0034333) and Davis et al (US Patent No: 6,509,323), further in view of Cheng et al (US Patent Publication

NO: US2004/0077595). Claims 10, 13-15, 26-28 recite a biodegradable copolymer comprising a polyethyleneimine linked to a cyclodextrin, wherein the polyethylenimine is a linear polymer having a molecular weight of less than 10,000 Daltons, and wherein the cyclodextrin is modified at no more than two positions by an agent to allow attachment to no more than two polyethylenimine molecules wherein the cyclodextrin is beta-cyclodextrin and the agent is beta-1,1'-carbonyldiimidazole (claim 10). The biodegradable copolymer is further limited wherein the copolymer contains up to about 35 PEI units (claim 13) between 5 and 25 PEI units (claim 14), or between 10 to 15 PEI units (claim 15).

32. Claims 19, and 26-28 recite a method for synthesizing a biodegradable copolymer comprising the steps of treating cyclodextrin with an agent to form a modified or activated cyclodextrin and adding the cyclodextrin to a low molecular weight polyethylenimine to form a biodegradable copolymer. The method is further limited wherein the cyclodextrin is beta-cyclodextrin wherein the agent is beta-1,1'-carbonyldiimidazole (claim 19) and the method is further limited wherein the copolymer contains up to about 35 PEI units (claim 26) or about 5 and 25 PEI units (claim 27) or about 10 to 15 PEI units (claim 28).

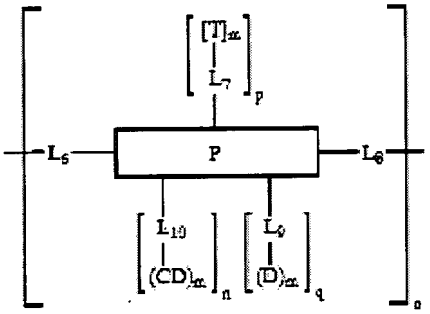
33. This rejection is based on the alternate reading in which the base claims 1 and 16 read on a copolymer comprising the structure:

PEI-PEI-CD-CD-PEI-PEI-CD-CD-PEI-PEI or CD-PEI-CD-PEI-CD-PEI

34. Kosak et al and Davis teach a copolymer comprising beta-cyclodextrin and a low molecular weight polyethyleneimine and methods of making said linear copolymer (see

above). Kosak and Davis do not teach that the activation agent is beta-1,1'-carbonyldiimidazole nor that the copolymer contains up to about 35 PEI, 5 and 25 PEI units or 10 to 15 PEI units.

35. Cheng et al (US Patent Publication No: US2004/0077595) teaches compositions and methods of making said compositions comprising cyclodextrin polymers for carrying drugs and other active agents (see abstract). Cheng teaches that his copolymers reduce toxicity and increased stability of the therapeutics it carries (see abstract). Specifically Cheng teaches copolymers comprising the formula II according to claim 3 wherein CD is a cyclodextrin, P is a monomer unit of a polymer, and D represents a therapeutic agent:



36. Cheng teaches that the polymer can be polyethylenimine with a molecular weight of 25,000 (example 25), and that the copolymer (o) of formula II comprises 1-30,000 polymer units (claim 3), and more specifically, "0 represents an integer in the range of 1 to about 30,000 (preferably <25,000, <20,000, <15,000, <10,000, <5,000, <1,000, <500, <100, <50, <25, <10, or even <5)" (paragraph 0029). Cheng teaches that the polymer can be linear (paragraph 0009) "and may be formed via polycondensation of

cyclodextrin-containing monomers, copolymerization between one or more cyclodextrin-contianing monomers and one or more comonomers which do not contain cyclodextrin moieties" (paragraph 0009).

37. Cheng further teaches:

For example, the polymer may be a water-soluble, **linear cyclodextrin polymer produced by providing at least one cyclodextrin derivative modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin derivative with a linker** having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties **to form covalent bonds between the linker and the cyclodextrin derivative, whereby a linear polymer comprising alternating units of cyclodextrin derivatives and linkers is produced**. Alternatively the polymer may be a water-soluble, linear cyclodextrin polymer having a linear polymer backbone, which polymer comprises a plurality of substituted or unsubstituted cyclodextrin moieties and linker moieties in the linear polymer backbone, wherein each of the cyclodextrin moieties, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two of said linker moieties, each linker moiety covalently linking two cyclodextrin moieties. In yet another embodiment, the polymer is a water-soluble, linear cyclodextrin polymer comprising a plurality of cyclodextrin moieties covalently linked together by a plurality of linker moieties, wherein each cyclodextrin moiety, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two linker moieties to form a linear cyclodextrin polymer.

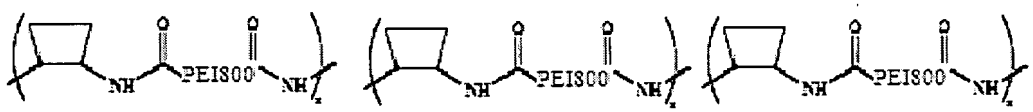
The linker group(s) may be an alkylene chain, a polyethylene glycol (PEG) chain, polysuccinic anhydride, poly-L-glutamic acid, **poly(ethyleneimine),** an oligosaccharide, an amino acid chain, or any other suitable linkage." (page 12, paragraphs 0174-0175) (emphasis added).

38. Cheng teaches that the cyclodextrin is beta-cyclodextrin (page 6, paragraph 0082) and is modified to allow conjugation (paragraph 0083). Cheng teaches that the copolymer can be treated with carbonyldiimidazole (beta-1,1'-carbonyldiimidazole) in order to add amine groups (page 30, paragraph 0309) which would result in a net positive charge. Cheng further teaches that the copolymer is conjugated via a carbonyl group (page 9, paragraph 0112), and the copolymer comprises ester bonds (claim 11).

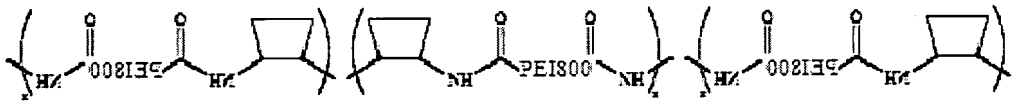
Furthermore, Cheng teaches that the copolymer compound comprises therapeutic agents such as nucleic acids (page 7, paragraph 0094).

39. A skilled artisan would have been motivated to combine the teaching of Kosak et al and Davis on a biodegradable copolymer comprising beta-cyclodextrin and a low molecular weight polyethyleneimine, wherein the beta-cyclodextrin is modified at no more than two positions by an activating agent and methods of making said linear copolymer that is useful for delivering therapeutics including nucleic acids further with the teaching of Cheng on a linear copolymer comprising cyclodextrin and PEI, with an agent of beta-1,1'-carbonyldiimidazole, further comprising subunits of up to about 35 PEI, 5 and 25 PEI units or 10 to 15 PEI units that is also useful for delivering therapeutics including nucleic acids for the expected benefit of smaller polymer units capable to delivering the therapeutics.

40. A polymer comprising a low molecular weight PEI copolymer as taught by Kozak, and an activated linear cyclodextrin of David (who teaches a polyethylene polymer can be exchanged for the PEG of his example) in view of Cheng would have the structure:



Or



41. It would have been obvious to the skilled artisan to combine the teaching of a Kosak et al and Davis et al on a biodegradable copolymer comprising beta-cyclodextrin and a low molecular weight polyethyleneimine, wherein the beta-cyclodextrin is modified at no more than two positions by an activating agent and methods of making said linear copolymer that is useful for delivering therapeutics including nucleic acids further with the teaching of Cheng on a linear copolymer comprising cyclodextrin and PEI, with an agent of beta-1,1'-carbonyldiimidazole, further comprising subunits of up to about 35 PEI, 5 and 25 PEI units or 10 to 15 PEI units that is also useful for delivering therapeutics including nucleic acids because Cheng teaches have reduced toxicity, thereby improving the copolymers of Kosak and Davis. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Response to art rejection arguments

42. In the response dated 3/21/07 applicant presents arguments against the 102 (b) rejection over Kosak et al from the office action dated 11/21/07.

43. Applicant traverses the rejection and presents arguments stating, "Kosak teaches polymerized CD without intervening PEI units. Kosak does not describe a linear copolymer of units comprising CD linked to PEI, as required by instant claims 1 and 16" and "As the CD polymers are synthesized before interacting with PEI, PEIs are linked to side chains to the CD polymers" and "Kosak fails to teach or suggest that the PEI-CD

copolymer can be used for gene delivery either in vitro or in vivo as in the present invention"

44. Applicant's arguments have been fully considered but they are not fully persuasive. The Examiner agrees that Kosak does not specifically teach a linear copolymer. However, The examiner disagrees with Applicant's arguments that PEIs are linked only to side chains and that Kosak does not teach or suggest that the PEI-CD copolymer can be used for in vitro or in vivo of the present invention (pages 13-14 of applicant's response).

45. Firstly, the Examiner disagrees that Kosak only teaches that the PEI can be linked to the side chains of the CD (see above rejections). Kosak specifically teaches that conjugation of linkers and molecules can occur before, during or after polymerization, and specifically teaches that PEI is one molecule that can be conjugated to the CD molecules:

> Capping is a type of derivatizing defined herein as **coupling any suitable chemical** "capping substance" **to two** or more **sites on the CD molecule** so that the substance spans the area between the coupled sites. Preferably, the capping substance spans across one of the end openings of the CD molecule and thereby stops the passage of a guest molecule through the capped CD molecule. Paragraph 0206
>
> **The CD's used herein can be suitably complexed with one or more guest molecules and/or derivatized and/or capped** before, **during** or after their **incorporation into the water-soluble CD polymer carrier of the instant invention**. In addition, the derivatizing and/or capping can be a done to produce CD's with the desired substances **coupled to specific locations on the CD molecule**. (paragraph 0206 and 0208)
>
> Preferably, **the capping substance is coupled** at the primary or secondary "end" of the CD molecule, **forming a bridge across** either (or both) opening(s) that includes suitable hydrophobic groups in the capping substance. **The capping substances can be coupled directly to available hydroxyls on the CD, or they can be coupled to** suitable functional groups such as; diamino (or triamino), compounds to iodinated CD, or azido compounds to sulfonylated hydroxyls, and/or through **"spacers"** added to the CD. Paragraph 0210 of Kosak.

Alternatively, other amino compounds have been coupled to the oxidized CD such as hydrazine, adipic add dihydrazide, glutamic acid, beta-phenylethylamine, laurylamine and cystamine. **Many other useful amino compounds can be coupled to the oxidized CD or CD-block such as** polypeptides, 6-amino-N-hexanoic acid, arginine, protamines, N-(2-aminoethyl)-1,3-propanediamine (AEPD), **polyethylenimine (PEI)** and nucleic acids. Paragraph 0284. (Emphasis Added).

46. Secondly, the Examiner disagrees that the PEI-CD copolymer can be used for gene delivery either in vitro or in vivo of the present invention. This argument is directed towards limitations not found in the current claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., in vivo or in vitro) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). However, for the purposes of clarity, Kosak teaches his copolymers of his invention has several advantages, which reads on both in vivo and in vitro work:

47. The advantages or the water soluble cyclodextrin polymer carrier are: (1) Drugs can be used that are designed for efficacy without solubility or conjugation requirements. (2) Drugs can be delivered as macromolecules and released within the cell. (3) Drugs can be targeted by coupling the carrier to biorecognition molecules (paragraphs 0012-0015).

48. Kosak further goes on to teach that embodiments of drugs includes nucleic acids:

49. For the purposes of this invention, certain nucleic acids are preferred as a specific class of active agents directed against viral and other microbial diseases, against cancers, autoimmune and genetic diseases. Specific nucleic acid active agents include any anti-bacterial, anti-cancer, anti-fungal, anti-viral, anti-parasitic and anti-protozoan nucleic acids. The also include specific DNA sequences used for gene therapy. Nucleic...acid active agents include all types of RNA (including messenger RNA), all types of DNA, and oligonucleotides including probes and primers used in the polymerase chain reaction (PCR), hybridizations or DNA sequencing (paragraph 0038-0040).

50. Thus Kosak does teach both in vivo and in vitro uses for the polymers of carriers of nucleic acids in his invention.

51. Applicant further presents arguments which attempt to further distinguish the instant application from Kosak:

> The instant biodegradeable copolymers are prepared in such a way that the CD molecules are covalently linked through low MW PEI to form a CD-PEI copolymer wherein the CD molecules and the PEI molecules make up the copolymer backbone.
> Low MW PEIs or CD molecules have a higher MW than the spacers Kosak used and, as such, are not biocleavable, i.e., they are much more stable and are best described as being biodegradable.
> Most importantly, because of the design, the backbone of the instant copolymers contains two monomer units: low MW PEI and CD. The present inventors have created a way to control the reaction conditions to make CD interact with only two PEI molecules giving the so called AB block copolymers (page 14 of applicant's response).

52. Firstly, these arguments are directed towards limitations not found in the current claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., placement of PEI and CD in the backbone, monomer units, block copolymers etc) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns,* 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

53. Secondly, the current claims are drawn to PEI's having less than 10,000 Daltons. Thus any PEI having a molecular weight of less than 10,000 Daltons reads on the current claims. Kosak teaches his PEI has a molecular weight of 800.

54. In the response dated 3/21/07 applicant presents arguments against the 102 (e) rejection over Cheng et al from the office action dated 11/21/07.

55. Applicant traverses the rejection and presents arguments stating, "CD molecules were conjugated to PEI25kDA. Cheng fails to teach how to use PEI or CD linkers to form copolymers having PEI and CD as linkers to form copolymers in the backbone, as presently claimed" (page 15 of applicant's response).

56. The examiner agrees that Cheng does not teach PEI with a molecular weight of less than 10,000 Daltons, however the examiner disagrees with the statement that "Cheng fails to teach how to use PEI or CD linkers to form copolymers having PEI and CD as linkers to form copolymers in the backbone, as presently claims.

57. Applicant is respectfully directed to Cheng's disclosure:

For example, the polymer may be a water-soluble, **linear cyclodextrin polymer produced by providing at least one cyclodextrin derivative modified to bear one reactive site at each of exactly two positions, and reacting the cyclodextrin derivative with a linker** having exactly two reactive moieties capable of forming a covalent bond with the reactive sites under polymerization conditions that promote reaction of the reactive sites with the reactive moieties **to form covalent bonds between the linker and the cyclodextrin derivative, whereby a linear polymer comprising alternating units of cyclodextrin derivatives and linkers is produced**. Alternatively the polymer may be a water-soluble, linear cyclodextrin polymer having a linear polymer backbone, which polymer comprises a plurality of substituted or unsubstituted cyclodextrin moieties and linker moieties in the linear polymer backbone, wherein each of the cyclodextrin moieties, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two of said linker moieties, each linker moiety covalently linking two cyclodextrin moieties. In yet another embodiment, the polymer is a water-soluble, linear cyclodextrin polymer comprising a plurality of cyclodextrin moieties covalently linked together by a plurality of linker moieties, wherein each cyclodextrin moiety, other than a cyclodextrin moiety at the terminus of a polymer chain, is attached to two linker moieties to form a linear cyclodextrin polymer.

The linker group(s) may be an alkylene chain, a polyethylene glycol (PEG) chain, polysuccinic anhydride, poly-L-glutamic acid, **poly(ethyleneimine),** an oligosaccharide, an amino acid chain, or any other suitable linkage." (page 12, paragraphs 0174-0175) (emphasis added).

58. Thus, the works by Kosak and Cheng are still relevant to the current claims in part.

Conclusion

59. No claims are allowed.

60. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kam/05/23/07

DANIEL M. SULLIVAN, PH.D.
PRIMARY EXAMINER